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(54) Title: ANALGESIC USE OF N-L-α-ASPARTYL-L-PHENYLALANINE 1-METHYL ESTER

(57) Abstract

N-L-α-aspertyl-L-phenylalanine 1-methyl ester and/or its derivatives has been found to have analgesic pain relieving properties in both humans and animals. It has been found to be especially effective in relieving pain associated with osteoarthritis and multiple sclerosis. It can be administered by itself or in combination with other analgesics. When given in combination with other analgesics, *N*-L-α-aspartyl-L-phenylalanine 1-methyl ester and/or its derivatives helps to alleviate the detrimental side effects of other analgesic medications by lowering the d sage requirements for pain relief.

Arthritis

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ANALGESIC USE OF *N*-L-α-ASPARTYL-L-PHENYLALANINE 1-METHYL ESTER

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of copending U.S. Application No. 08/590,409 filed January 25, 1996, which claims the benefit of copending U.S. Provisional Application No. 60/000,479 filed June 23, 1995.

TECHNICAL FIELD

The present invention relates to pain relieving composition and a method for use.

BACKGROUND OF THE INVENTION

Pain is the most common symptom for which patients seek medical assistance. In the case of incurable diseases, treatment for pain may last for extended periods of time. Pain is both a physical and an emotional experience which differs greatly from one individual to another. Although subjective, most pain is associated with tissue damage and has a physiological basis.

Pain can be either acute or chronic. Acute pain is generally caused by sudden injury, tissue damage, or infection for which the cause is easily found. Chronic pain, however, is the pain of pathological conditions and often difficult to isolate and treat. Chronic pain is routinely defined as pain of over six months duration.

For patients suffering from chronic pain, the autonomic nervous system adapts to the pain and evidences of autonomic hyperactivity such as tachycardia, hypertension, diaphoresis, mydriasis, and pallor disappear, leaving the physician to rely on the patient's subjective complaints in assessing chronic pain.

In the management of chronic pain, some types of pain permit treatment of the underlying disorder, i.e., radiation treatment for pain cause by bone cancer. In some cases, a particular treatment is given for a specific type of pain, i.e., treatment of trigeminal neuralgia or glossopharyngeal neuralgia with

carbamazepine, reflex sympathetic dystrophies with local anesthetic, postherpetic neuralgia with direct stimulation.

In many patients, however, the pain is chronic and the physician can neither treat the underlying disturbance nor prescribe a specific therapy for that type of pain. For example, osteoarthritis is a joint disease characterized by degeneration and loss of articular cartilage and by osteophyte formation, or bony outgrowth of subchondral bone. The disease is slowly progressive, leading to chronic pain and stiffness and gradually to increasing dysfunction of the affected joint. The incidence of the disease increases with age and affects three times as many women as men.

Chronic joint pain, swelling, creaking, and stiffness are the most prominent symptoms of osteoarthritis. The disease commonly affects the distal interphalangeal joints of the hands, resulting in bone enlargements often accompanied by inflammation and pain. Weight bearing joints such as the neck, lower back, knees and hips are often affected by this type of arthritis.

Another major symptom of osteoarthritis is loss of articulation of the joint. Weakness and shrinkage of surrounding muscles may occur if pain prevents the joint from being used regularly. As movement of an affected joint becomes severely limited, the sufferer experiences loss of functionality of the joint. In the

case of osteoarthritis of the hip or knees, ambulation becomes impaired.

Although osteoarthritis is the most common of the rheumatic diseases, its pathogenesis is not well understood, and currently there is no treatment that will retard or reverse pathological processes in the disease. The only treatment available to osteoarthritis sufferers has involved symptomatic treatment through analgesics for pain and nonsteroidal anti-inflammatory agents for reduction of joint inflammation. An injection of a corticosteroid may also be administered to a painful joint.

Chronic pain is also associated with multiple sclerosis (MS), also known as disseminated or insular sclerosis, a disease of the central nervous system (CNS) characterized by widespread patches of demyelination in the brain and spinal cord. The disease occurs worldwide in about 10-60 persons per 100,000 with the age at onset occurring at about 20-40 years, and appears to affect females more often than males. While MS is generally chronic and relapsing, fulminating attacks occur, and as many as 30% of the patients progress steadily from the onset.

Although multiple sclerosis is the most common demyelinating disease, its cause is unknown, and there is no treatment to retard or reverse the pathological processes of the disease. There is no specific therapy recommended because spontaneous remissions make treatment difficult to evaluate. The only treatment

available to multiple sclerosis patients include corticosteroid therapy (e.g., prednisone or dexamethasone) until manifestations remit, and symptomatic treatment such as baclofen for spasticity and pain relievers such as analgesics and opiates.

There are several types of drugs used to decrease chronic pain. Analgesics are drugs used to decrease pain without causing loss of consciousness or sensory perception. There are two basic classes of analgesics: anti-inflammatory, routinely prescribed for short-term pain relief and for modest pain, and opioids used for either short-term or long term pain relief of severe pain. The anti-inflammatory analgesics generally provide analgesia, anti-inflammation, and antipyretic action. It has been reported that the mechanism of action may be to provide inhibition of the synthesis of prostaglandins. W.W. Douglas, "Polypeptides - angiotensin, plasma kinins, and other vasoactive agents; prostaglandins," *The Pharmacological Basis of Therapeutics*, 9th edition, L.S. Goodman and A. Gilman (eds.), MacMillan Publishing Co., Inc., New York, 1975. Prolonged use of anti-inflammatory analgesics have been known to cause gastrointestinal problems.

The opioid analgesics, or narcotics, include all natural or synthetic chemical compounds closely related to morphine and are thought to activate one or more receptors on brain neurons. Opioid analgesics have serious side effects and thus are used with discrimination. These side effects include: 1)

tolerance, which requires gradually increasing doses to maintain analgesia; 2) physical dependence, which means that the narcotics must be withdrawn gradually if they are discontinued after prolonged use; 3) constipation, which requires careful attention to bowel function, including use of stool softeners, laxatives, and enemas; and 4) various degrees of somnolence, or drowsiness, which requires adjustments in dosages and dose scheduling, or possibly varying the type of narcotic to find one better tolerated by the patient.

It has been reported that various treatments for pain are additive and should be used together rather than separately. For example, the combination of aspirin or acetaminophen and codeine is often prescribed to provide pain relief stronger than codeine by itself. Certain antidepressants prescribed for depression have been recommended as an analgesic adjuvant.

While pain management has been a problem faced by physicians for many years, available pain medications have ameliorated, but not alleviated the problem of pain treatment. A significant problem remains in that detrimental side effects are often caused by pain-relieving medications as detailed above. Thus, there remains a continuing need for alternative pain therapy regimens which would address the need for pain reduction but also reduce these side effects.

Surprisingly, it has now been discovered that *N*-L-α-aspartyl-L-phenylalanine 1-methyl ester and

derivatives have analgesic properties, relieving pain and restoring function of soft tissues, muscles, ligaments, tendons, bones, and joints. Further, when taken in combination with other analgesic agents, *N*-L-α-aspartyl-L-phenylalanine 1-methyl ester provides an additive analgesic effect. The detrimental side effects inherent in pain therapy known to the art can be reduced through the use of *N*-L-α-aspartyl-L-phenylalanine 1-methyl ester in pain therapy and management.

SUMMARY OF THE INVENTION

In one aspect of the invention, *N*-L-α-aspartyl-L-phenylalanine 1-methyl ester or its derivatives or both are used in a method for decreasing pain in a mammal.

In another aspect, *N*-L-α-aspartyl-L-phenylalanine 1-methyl ester or its derivatives or both are used in combination with an anti-inflammatory analgesic drug of other composition in a pain treatment regimen.

In another aspect, *N*-L-α-aspartyl-L-phenylalanine 1-methyl ester or its derivatives or both are used in combination with an opioid analgesic in a pain treatment regimen.

In yet another aspect, *N*-L-α-aspartyl-L-phenylalanine 1-methyl ester or its derivatives or both are used in treating osteoarthritis.

Another aspect of the invention concerns pharmaceutical dosage form containing *N*-L-α-aspartyl-L-phenylalanine 1-methyl ester or its derivatives or both.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph depicting the average time required to ascend and descend stairs for the APM and control treatment groups measured over time.

Fig. 2 is a graph depicting the average pain experienced by the APM and control treatment groups upon ascending and descending stairs measured over time.

Fig. 3 is a graph depicting the average rest pain experienced by the APM and control treatment groups taken after a one hour rest period following ascending and descending stairs measured over time.

Fig. 4 is a graph depicting the difference between stair pain and rest pain experienced by the APM and control treatment groups upon ascending and descending stairs measured over time.

Fig. 5 is a graph depicting the average distance walked by the APM and control treatment groups measured over time.

Fig. 6 is a graph depicting the average pain experienced by the APM and control treatment groups upon walking for five minutes measured over time.

Fig. 7 is a graph depicting the average grip strength for the APM and control treatment groups measured over time.

Fig. 8 is a graph depicting the average gripping pain experienced by the APM and control treatment groups measured over time.

Fig. 9 is a graph depicting the average bleeding time before and after treatment with APM or placebo.

Fig. 10 is a graph depicting the average amount of blood loss before and after treatment with APM or placebo.

DETAILED DESCRIPTION

Chronic pain has been shown to be associated with various pathological conditions such as osteoarthritis, inflammation, multiple sclerosis, and myocardial infarction. It has now been found that *N*-L-α-aspartyl-L-phenylalanine 1-methyl ester (APM), which has been sold under the trade name of ASPARTAME™ (G.D. Searle & Company, Chicago, IL) and its derivatives offers medicinal qualities beneficial in the treatment of chronic pain in mammals. One can use an effective amount of APM to effect a reduction in perceived pain by the recipient within one hour of dosage. An effective amount of APM which can effect pain relief after one dose is from about 80 milligrams to about 320 milligrams. A preferred range is from about 80 milligrams to about 160 milligrams. Most preferred is about 160 milligrams. The dosage can be repeated over time for continued relief, preferably at 160 milligrams every 4 hours. APM can also be administered together with other analgesics such as acetaminophen, phenacetin, aspirin, ibuprofen, phenylbutazone, indomethacin and derivatives, opiates and derivatives, piroxacam, and steroidal and nonsteroidal anti-inflammatory agents, providing additive analgesic properties.

APM can be administered orally, parenterally, intraperitoneally, or sublingually. It can be administered via ingestion of a food substance containing APM in a volume sufficient to achieve

therapeutic levels. Alternatively, it can be enclosed in capsules, compressed into tablets, microencapsulated, entrapped in liposomes, in solution or suspension, alone or in combination with a substrate immobilizing material such as starch or poorly absorbable salts. Pharmaceutically compatible binding agents and/or adjuvant materials can be used as part of a composition. Tablets or capsules can contain any of the following ingredients, or compounds of similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; and excipient such as starch or lactose, an integrating agent such as alginic acid, corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; and additional sweetening and flavoring agents. When a capsule form is used the liquid carrier such as a fatty oil may be used. Capsules and tablets can be coated with sugar, shellac and other enteric agents as is known. APM can also be in a controlled-release formulation.

APM is available commercially. Its preparation is also disclosed in U.S. Patent No. 3,492,131. It is believed that various modifications can be made to the APM molecule and the resulting derivatives will also have utility in the claimed invention. Since the 1-methyl ester portion of the molecule is not believed to contribute to the analgesic activity of the molecule, *N*-L-α-aspartyl-L-phenylalanine itself or other lower alkyl esters are believed to be effective. Other

possible analgesic physiologically acceptable derivatives are believed to include N-acyl-L-(beta-substituted)- aspartyl-L-phenylalanine lower alkyl esters and N-acyl-L-(beta-substituted)-aspartyl-L-phenylalanine. Chemical modifications made to the APM molecule which do not reduce the analgesic physiologically active properties disclosed herein thus fall within the scope of this invention.

Example 1: Osteoarthritis

In a well-controlled double-blind crossover study, patients suffering from osteoarthritis were given the tasks of climbing stairs, walking, and hand gripping, all of which are known to cause chronic pain in osteoarthritic patients, following treatment with either APM or a placebo. The study was performed twice for all patients, and prior to each study, all other analgesics were withheld for twenty-four hours. During the first study, one test group of eleven patients were randomly administered 4 tablets of either aspartame (76 milligrams; 19 milligrams/tablet) or placebo, and another test group of nine patients were randomly given 8 tablets of either aspartame (152 milligrams; 19 milligrams/tablet) or placebo. During the second study, each patient was given the same number of tablets but were given the opposite medication from what they had received in the first study. Following each test, data analysis of the recovered information was completed using non-parametric analyses of variance

and distribution free assessments of the measured variable.

Stair Climbing

Twenty osteoarthritic patients divided into groups of nine and eleven each were asked to ascend and descend one flight of stairs, making a total of three trips with one-hour rest periods between trips. Right after the first baseline trip, patients were administered the test medication. All patients then made three subsequent trips up and down the stairs. Table I and Fig. 1 present an objective measurement of performance with respect to the time required for each patient to ascend and descend one flight of stairs. The mean results show that over time the 4-tablet APM group decreased the stair time, with a 9.6% decrease for the last trip. For the 8-tablet APM group, a decrease of 11.9% was observed for the second trip after dosing and 6.9% for the last trip. After administration of the placebo, the 4-tablet placebo group showed a decrease in stair time of 6.5% for the first and second trips after dosing, and 3.7% for the last trip. The 8-tablet placebo group showed a gradual increase in stair time with a maximum increase of 2% for the last trip.

A subjective measurement of stair pain was made by administering a visual analog pain assessment to the patients. A baseline assessment for various joints, usually three joints, was taken one hour prior to the first baseline trip, and the assessment was then

Table I: Stair Time with and without APM

Subject #	Stair Climb Time (min) Hours after Treatment			
	0	1	2	3
Control group - 4 tablets placebo				
1	1.04	0.59	0.59	1.01
2	0.92	0.99	0.97	0.96
3	1.19	1.12	1.10	1.15
4	1.00	1.03	1.04	1.04
5	0.90	0.91	0.94	0.98
6	2.09	1.50	1.51	1.56
7	0.79	0.79	0.80	0.81
8	1.28	1.27	1.23	1.24
9	1.25	1.26	1.26	1.26
10	0.72	1.02	1.01	0.80
11	0.56	0.58	0.54	0.55
mean	1.07	1.00	1.00	1.03
APM group - 4 tablets APM				
1	1.05	1.01	1.00	1.01
2	0.96	0.96	0.93	0.88
3	1.10	1.08	1.04	1.02
4	1.10	1.10	1.07	1.06
5	0.90	0.91	0.89	0.92
6	2.07	2.10	2.16	1.54
7	0.78	0.79	0.79	0.78
8	1.36	1.30	1.28	1.33
9	1.23	1.25	1.24	1.25
10	1.01	1.02	1.02	1.02
11	1.07	1.03	1.01	0.59
mean	1.15	1.14	1.13	1.04

Subject #	Stair Climb Time (min) Hours after Treatment			
	0	1	2	3
Control group - 8 tablets placebo				
12	0.94	0.94	0.91	0.93
13	0.90	0.92	0.90	0.96
14	1.44	1.43	1.51	1.56
15	0.49	0.51	0.54	0.58
16	1.24	1.25	1.25	1.22
17	1.07	1.07	1.13	1.13
18	1.14	1.11	1.09	1.10
19	0.81	0.84	0.83	0.84
20	1.15	1.08	1.08	1.05
mean	1.02	1.02	1.03	1.04
APM group - 8 tablets APM				
12	0.94	0.92	0.89	0.86
13	0.87	0.88	0.89	0.90
14	1.45	1.42	1.35	1.44
15	0.50	0.55	0.56	0.51
16	1.33	1.25	1.27	1.25
17	1.00	1.03	0.55	0.59
18	1.14	1.16	1.08	1.08
19	0.84	0.88	0.86	0.83
20	1.06	1.02	0.58	1.00
mean	1.01	1.01	0.89	0.94
Total mean score by treatment group				
Control	1.05	1.01	1.01	1.04
APM	1.09	1.08	1.02	0.99

repeated for each of the four trips. Each patient made an assessment under a nurse's supervision (same nurse throughout study) as to the amount of pain involved on a scale marked with increments for none, a little, more, a lot, and most. A numerical conversion of the marks on the scale in millimeters taken as the distance from the absence of pain mark were made. The representation of this assessment scale where the lower the number the lesser the pain, and the higher the number, the greater the pain is given in Table II and Fig. 2 as an average value for all rated joints. Referring to the mean, there was a marked decrease in the amount of pain associated with ascending and descending stairs in the APM groups in comparison to that in the placebo groups. The 4-tablet placebo group showed increased pain over the pre-climbing baseline assessment for each trip; however, while the 4-tablet APM group also experienced increased pain over the pre-climbing baseline assessment for the first two trips, they had decreased pain below or just above the pre-climbing baseline assessment for the last two trips.

Table III provides pain assessment measurements for the most sensitive joint for some of the patients taken at one hour and two hours after treatment. For the 4-tablet treatment groups, the placebo group showed a slight increase in pain (2.2%), while the APM group experienced a 52.2% decrease in pain. The 8-tablet APM group also experienced a significant decrease in pain

Table II: Stair Pain with and without APM

Subject #	Stair Pain (relative numerical scale) Hours after Treatment				
	-1	0	1	2	3
Control group - 4 tablets placebo					
1	27	49	33	42	36
2	62	102	119	91	74
3	51	85	67	110	73
4	31	73	25	32	31
5	42	59	38	73	58
6	93	117	118	126	127
7	24	81	97	89	88
8	41	22	31	28	21
9	31	46	64	45	75
10	55	72	78	88	85
11	36	48	50	31	36
mean	44.82	68.55	65.45	68.64	64.00
APM group - 4 tablets APM					
1	45	47	48	36	22
2	24	80	91	32	38
3	106	130	130	73	73
4	79	63	70	40	42
5	41	71	56	56	44
6	46	95	130	101	130
7	28	87	87	56	74
8	59	28	30	28	62
9	94	56	47	30	30
10	67	83	96	91	105
11	36	45	49	52	24
mean	56.82	71.36	75.82	54.09	58.55

Subject #	Stair Pain (relative numerical scale) Hours after Treatment				
	-1	0	1	2	3
Control group - 8 tablets placebo					
12	33	66	60	51	59
13	22	40	26	30	24
14	35	74	115	116	118
15	45	74	21	33	50
16	50	52	50	51	56
17	22	28	26	22	21
18	62	74	92	77	74
19	8	49	63	49	83
20	43	45	33	20	21
mean	35.56	55.78	54.00	49.89	56.22
APM group - 8 tablets APM					
12	42	72	71	51	53
13	31	31	39	31	31
14	69	97	84	85	117
15	33	35	23	31	33
16	53	52	54	53	54
17	39	31	15	21	17
18	25	48	65	49	56
19	57	78	63	72	74
20	34	37	26	14	14
mean	42.56	53.44	48.89	45.22	49.89
Total mean score by treatment group					
Control	40.65	62.80	60.30	60.20	60.50
APM	50.40	63.30	63.70	50.10	54.65

Table III: Stair Pain of Most Sensitive Joint with and without APM

Subject #	Stair Pain (relative numerical scale) Hours after Treatment	
	1	2
Control group - 4 tablets placebo		
1	24	43
2	113	105
3	63	92
4	25	32
5	21	57
6	149	149
7	97	77
8	16	21
9	73	35
10	-	-
11	33	17
mean	61.40	62.80
APM group - 4 tablets APM		
1	53	35
2	107	53
3	130	16
4	104	46
5	56	22
6	150	106
7	75	39
8	45	26
9	73	37
10	-	-
11	32	14
mean	82.50	39.40

Subject #	Stair Pain (relative numerical scale) Hours after Treatment	
	1	2
Control group - 8 tablets placebo		
12	48	39
13	26	38
14	-	-
15	-	-
16	-	-
17	-	-
18	129	93
19	86	58
20	33	15
mean	64.40	48.60
APM group - 8 tablets APM		
12	71	11
13	55	39
14	-	-
15	-	-
16	-	-
17	-	-
18	32	15
19	86	72
20	36	8
mean	56.00	29.00
Total mean score by treatment group		
Control	62.40	58.07
APM	73.67	35.93

(48.2%), compared to a 24.5% decrease in pain for the 8-tablet placebo group.

An evaluation of pain was also measured using the visual analog pain assessment method by the patient at the end of each rest period (Table IV and Fig. 3). While the average rest pain generally increased for both placebo groups, the 4-tablet APM group experienced a 12.2%, 16.5%, and 10.4% decrease in rest pain from pretreatment over time, while the 8-tablet APM group, a 2.3%, 36.8% and 14.6% decrease. In Table V and Fig. 4, the mean difference between stair pain and rest pain for each patient at each time period is given, showing that the mean difference of the APM groups was lower than the placebo groups. As indicated by the negative numbers, some patients in both groups experienced greater rest pain than stair climb pain.

Walking Distance

Chronic pain was examined in respect to distance walking at a comfortable speed for a five minute period. A pre-walking baseline pain assessment was performed. After establishing a baseline walking distance, the 4- and 8-tablet APM groups were given 76 milligrams and 152 milligrams APM, respectively, while the 4- and 8-tablet control groups were given the appropriate number of placebo tablets. After resting for one hour, the patients repeated the 5-minute walking procedure three times with one hour rest

Table IV: Rest Pain with and without APM

Subject #	Rest Pain (relative numerical scale) Hours after Treatment			
	0	1	2	3
Control group - 4 tablets placebo				
1	27	31	32	45
2	62	79	36	48
3	51	10	30	15
4	31	46	30	30
5	42	54	40	41
6	93	116	127	129
7	24	39	42	40
8	41	35	23	16
9	31	31	48	58
10	55	70	73	80
11	36	35	32	25
mean	44.82	49.64	46.64	47.91
APM group - 4 tablets APM				
1	45	37	45	17
2	24	50	77	78
3	106	25	14	30
4	79	68	56	40
5	41	40	39	41
6	46	77	94	99
7	28	9	8	39
8	59	49	25	27
9	94	77	32	24
10	67	80	89	96
11	36	38	43	69
mean	56.82	50.00	47.45	50.91

Subject #	Rest Pain (relative numerical scale) Hours after Treatment			
	0	1	2	3
Control group - 8 tablets placebo				
12	33	34	16	14
13	22	24	28	32
14	35	78	115	118
15	45	19	32	32
16	50	53	50	50
17	22	19	18	24
18	62	35	30	34
19	8	8	8	10
20	43	36	26	24
mean	35.56	34.00	35.89	37.56
APM group - 8 tablets APM				
12	42	58	32	38
13	31	32	28	33
14	69	73	53	86
15	33	20	19	27
16	53	54	52	52
17	39	35	20	16
18	25	33	12	20
19	57	39	9	39
20	34	30	17	16
mean	42.56	41.56	26.89	36.33
Total mean score by treatment group				
Control	40.65	42.60	41.80	43.25
APM	50.40	46.20	38.20	44.35

Table V: Stair Pain v. Rest Pain with and without APM

Subject #	Stair Pain Minus Rest Pain Hours after Treatment			
	0	1	2	3
Control groups - 4 or 8 tablets placebo				
1	22	1	10	-9
2	40	40	55	26
3	34	57	80	58
4	42	-21	2	1
5	17	-16	33	17
6	24	2	-1	-2
7	57	58	47	48
8	-19	-4	5	5
9	15	33	-3	17
10	17	8	15	5
11	12	15	-1	11
12	33	26	35	45
13	18	2	2	-8
14	39	37	1	0
15	29	2	1	18
16	20	-3	1	6
17	6	7	4	-3
18	12	57	47	40
19	41	55	41	73
20	2	-3	-6	-3
mean	23.05	17.65	18.40	17.25

Subject #	Stair Pain Minus Rest Pain Hours after Treatment			
	0	1	2	3
APM groups - 4 or 8 tablets APM				
1	2	11	-9	5
2	56	41	-45	-40
3	24	105	59	43
4	-16	2	-16	2
5	30	16	17	3
6	49	53	7	31
7	59	78	48	35
8	-31	-19	-2	35
9	-38	-30	-2	-4
10	16	16	2	9
11	9	11	9	-45
12	30	13	19	15
13	0	7	3	-2
14	28	11	84	116
15	2	3	12	6
16	-1	0	1	2
17	-8	-20	1	1
18	23	32	37	36
19	21	25	74	35
20	3	-4	-3	-2
mean	12.90	17.55	14.78	14.06

periods between trips. Table VI and Fig. 5 show the total distance walked in terms of feet traveled. The average distance walked in the control groups decreased slightly over time, with the mean varying from -0.5% to -2.2% from baseline. Comparatively, the average distance walked in the APM groups varied from -0.4% to 1.8% from baseline. Although the average distance walked decreased at one hour from baseline, there was an increase at 3 hours from baseline for both APM groups.

Walking distance pain was recorded via the visual analog pain assessment. A baseline assessment was taken one hour prior to the first baseline trip. The assessment was then repeated for each of the four trips. A relative numerical representation of this assessment scale where the lower the number the lesser the pain, and the higher the number, the greater the pain is given in Table VII and Fig. 6. The average distance pain after the four walks increased over the pre-walking baseline assessment by 22.7 to 42.8% for the 4-tablet control group, and 20.6% to 35.6% for the 8-tablet control group. Comparatively, the patients in the 4-tablet APM group showed an increase in average distance pain after the baseline walk (23.0%) and the first walk after dosing (21.8%), while the average distance pain decreased below the pre-walking baseline assessment by 1.1% after the second walk after dosing and then increased to 11.4% above the pre-walking

Table VI: Walking Distance with and without APM

Subject #	Walking Distance (feet) Hours after Treatment			
	0	1	2	3
Control group - 4 tablets placebo				
1	1035	1040	1055	1045
2	895	875	895	825
3	1000	980	1030	1000
4	1010	980	970	990
5	1100	1095	1095	1120
6	800	775	810	800
7	1325	1295	1310	1295
8	865	900	920	890
9	840	865	850	810
10	1175	1110	1085	1100
11	1150	1125	1105	1100
mean	1017.73	1003.64	1011.36	997.73
APM group - 4 tablets APM				
1	990	1000	1000	1000
2	880	840	835	870
3	1025	1080	1090	1100
4	910	885	900	910
5	1075	1075	1070	1060
6	755	770	785	810
7	1320	1320	1325	1310
8	820	825	890	885
9	830	810	850	880
10	1300	1235	1245	1220
11	1010	1000	1025	1070
mean	992.27	985.45	1001.36	1010.45

Subject #	Walking Distance (feet) Hours after Treatment			
	0	1	2	3
Control group - 8 tablets placebo				
12	935	930	920	910
13	1150	1160	1145	1120
14	780	785	760	770
15	1230	1250	1240	1170
16	900	930	940	920
17	1065	1025	995	1000
18	1095	1070	1085	1120
19	1350	1305	1300	1260
20	710	705	720	735
mean	1023.89	1017.78	1011.67	1000.56
APM group - 8 tablets APM				
12	980	930	910	1000
13	1120	1140	1115	1120
14	790	795	825	740
15	1210	1270	1260	1260
16	890	900	925	905
17	1000	995	960	1045
18	1075	1060	1070	1100
19	1285	1250	1250	1250
20	790	765	780	780
mean	1015.56	1011.67	1010.56	1022.22
Total mean score by treatment group				
Control	1020.50	1010.00	1011.50	999.00
APM	1002.75	997.25	1005.50	1015.75

Table VII: Walking Pain with and without APM

Subject #	Walking Pain (relative numerical scale) Hours after Treatment				
	-1	0	1	2	3
Control group - 4 tablets placebo					
1	27	43	49	43	37
2	62	81	80	53	53
3	51	83	25	16	53
4	31	46	38	22	22
5	42	87	87	71	39
6	93	95	116	128	128
7	24	57	57	77	76
8	41	63	43	35	56
9	31	39	57	56	65
10	55	70	70	70	73
11	36	40	38	34	33
mean	44.82	64.00	60.00	55.00	57.73
APM group - 4 tablets APM					
1	45	60	53	33	35
2	24	50	62	42	99
3	106	118	94	32	13
4	79	51	63	54	59
5	41	71	71	73	74
6	46	81	93	100	100
7	28	58	40	37	42
8	59	71	86	65	85
9	94	83	49	29	30
10	67	74	86	90	100
11	36	52	64	63	59
mean	56.82	69.91	69.18	56.18	63.27

Subject #	Walking Pain (relative numerical scale) Hours after Treatment				
	-1	0	1	2	3
Control group - 8 tablets placebo					
12	33	68	17	21	18
13	22	29	43	57	47
14	35	55	95	114	114
15	45	75	32	49	55
16	50	51	60	61	72
17	22	26	27	30	28
18	62	87	52	59	42
19	8	8	41	8	38
20	43	35	19	20	17
mean	35.56	48.22	42.89	46.56	47.89
APM group - 8 tablets APM					
12	42	41	30	40	40
13	31	47	48	47	46
14	69	95	84	84	96
15	33	38	31	36	27
16	53	54	61	54	56
17	39	35	28	27	24
18	25	49	55	29	44
19	57	75	11	40	39
20	34	44	24	16	13
mean	42.56	53.11	41.33	41.44	42.78
Total mean score by treatment group					
Control	40.65	56.90	52.30	51.20	53.30
APM	50.40	62.35	56.65	49.55	54.05

baseline assessment after the last walk. For the 8-tablet APM group, the average distance pain after the baseline walk increased over the pre-walking assessment by 24.8%; however, the average distance pain for the remaining three walks was right at or below the pre-walking baseline assessment.

Grip Strength

Grip strength was measured by placing the cuff into a cloth bag and filling with air to a resting pressure of 20 mmHg for easy gripping. Each patient gripped the cloth bag, and the increase in pressure registered as change in mmHg on the cuff was recorded. Following a baseline gripping measurement, the 4- and 8-tablet APM groups were given 76 milligrams and 152 milligrams APM, respectively, while the 4- and 8-tablet control groups were given the appropriate number of placebo tablets. After a one hour rest period, the gripping measurement was repeated three more times with a one hour rest period between each measurement. As shown in Table VIII and Fig. 7, both APM groups and the 4-tablet control group basically showed increasing grip strength over time. The 8-tablet control varied about 2% to 3% above and below baseline.

To determine average grip pain, a visual analog pain assessment was performed prior to the baseline gripping measurement and then repeated after each subsequent gripping measurement. In Table IX and Fig. 8, the mean data shows that within 2 hours after treatment, grip pain for both APM groups fell at or

Table VIII: Grip Strength with and without APM

Subject #	Grip Strength (mmHg) Hours after Treatment			
	0	1	2	3
Control group - 4 tablets placebo				
1	275	280	265	260
2	135	110	105	105
3	175	170	180	170
4	165	180	160	170
5	170	195	195	180
6	140	155	145	200
7	95	80	95	95
8	225	235	245	275
9	195	205	205	245
10	230	230	235	225
11	155	160	145	160
mean	178.18	181.82	179.55	189.67
APM group - 4 tablets APM				
1	240	235	255	250
2	65	85	80	105
3	75	135	155	180
4	115	135	165	145
5	140	165	170	160
6	120	100	140	160
7	95	110	95	105
8	190	240	215	210
9	270	275	295	265
10	170	165	155	155
11	180	170	170	170
mean	150.91	165.00	172.27	173.18

Subject #	Grip Strength (mmHg) Hours after Treatment			
	0	1	2	3
Control group - 8 tablets placebo				
12	85	90	100	100
13	155	155	170	160
14	165	160	145	135
15	150	140	145	140
16	230	210	210	215
17	180	180	190	225
18	165	150	170	165
19	85	90	105	85
20	55	75	90	90
mean	141.11	138.89	147.22	146.11
APM group - 8 tablets APM				
12	80	90	95	95
13	145	160	160	165
14	125	125	120	135
15	155	165	165	170
16	235	230	220	225
17	185	190	195	220
18	110	130	160	180
19	110	115	100	95
20	75	90	85	80
mean	135.56	143.89	144.44	151.67
Total mean score by treatment group				
Control	161.50	162.50	165.00	170.00
APM	144.00	155.50	159.75	163.50

Table IX: Grip Pain with and without APM

Subject #	Grip Pain (relative numerical scale) Hours after Treatment				
	-1	0	1	2	3
Control group - 4 tablets placebo					
1	48	79	50	59	51
2	-	-	-	-	-
3	85	25	22	84	84
4	46	59	21	21	15
5	-	-	-	-	-
6	47	82	105	86	82
7	75	76	76	100	77
8	19	19	18	17	16
9	24	42	42	41	25
10	43	70	80	87	85
11	37	54	45	35	45
mean	47.11	56.22	51.00	58.89	53.33
APM group - 4 tablets APM					
1	17	45	55	22	19
2	-	-	-	-	-
3	106	106	40	20	10
4	47	49	33	30	35
5	-	-	-	-	-
6	46	82	106	105	93
7	40	58	75	75	73
8	16	19	19	20	17
9	41	42	23	24	22
10	71	81	91	95	107
11	50	53	59	50	63
mean	48.22	59.44	55.67	49.00	48.78

Subject #	Grip Pain (relative numerical scale) Hours after Treatment				
	-1	0	1	2	3
Control group - 8 tablets placebo					
12	16	48	46	38	17
13	23	49	36	23	51
14	35	71	92	132	97
15	64	66	27	32	57
16	48	47	47	48	51
17	14	8	11	8	8
18	103	128	94	101	84
19	41	72	73	40	57
20	43	51	41	40	16
mean	43.00	60.00	51.89	51.33	48.67
APM group - 8 tablets APM					
12	16	43	74	39	15
13	23	23	22	20	20
14	34	31	71	71	72
15	32	35	40	48	56
16	18	17	16	20	17
17	9	13	21	24	7
18	88	75	90	47	71
19	98	97	72	74	73
20	75	70	36	22	17
mean	43.67	44.89	49.11	40.56	38.67
Total mean score by treatment group					
Control	45.06	58.11	51.44	55.11	51.00
APM	45.94	52.17	52.39	44.78	43.72

below the pre-gripping baseline assessment, while both control groups stayed at least 8% higher than the pre-gripping baseline assessment.

Overall, this study documents that use of APM was successful in relieving pain and that performance was measurably improved. Statistical assessments of measured variables suggests that the inference that the observed differences were due to chance is improbable at $p<0.05$ to $p<0.01$ or more.

Example 2: Osteoarthritis - Pain Alleviation

The analgesic properties of APM given over time was demonstrated in one osteoarthritic patient engaged in viewing a football game. The patient was in severe pain at the beginning of the game. However, upon consumption of six diet soft drinks through the course of the game (approximately 1 g APM over 3 hours), the patient experienced substantial pain relief and markedly increased joint mobility.

Example 3: Multiple Sclerosis - Pain Alleviation

In one example of the analgesic properties of APM in combination with other analgesic agents in relieving pain associated with multiple sclerosis, four tablets each containing 19.5 milligrams of APM was ingested by a patient with multiple sclerosis. The dosage was repeated at 100-120 milligrams every six hours. Upon administration of the APM, the patient's need for opiates for relief from pain dropped by 50%: one-half tablet

Percocet (Du Pont Pharmaceuticals, Wilmington, DE; each tablet containing 5 mg oxycodone hydrochloride and 325 mg acetaminophen) taken 2-3 times a day rather than one tablet taken 4 times a day. By combining APM with the opiate analgesic, the required dosage of the opiate analgesic was decreased, thereby lessening the negative side effects of the opiate analgesic such as constipation experienced by the patient.

Example 4: Alleviation of Pain Associated with Injury

APM provided pain relief for a 48 year old female (non-arthritic) who injured her heel and associated tendons and ligaments to the arch of the foot while running along rough terrain. At 12 hours after the injury, the patient walked with a severe limp. Approximately 4 packets (about 0.15 grams) APM mixed in orange juice was given to the patient on an empty stomach. Approximately 50 minutes later, the patient participated in a one mile hike without noticeable limp. A second 4-packet dose in orange juice was administered 5 hours later. Eight hours after start of treatment, the patient was walking without pain. The following morning, there was tenderness to thumb pressure but no pain while walking. Thirty-six hours after treatment, there was no pain and very little tenderness.

Example 5: Alleviation of Pain Associated with Back Surgery

Enrolled in a blind study, an osteoarthritis patient was taking a study compound for pain relief. Prior to back surgery, the patient discontinued using the study compound, but postoperatively, he resumed taking five tablets of the study compound unprescribed three times a day. On Day 1 after surgery, the patient took only one prescribed p.r.n. pain tablet and discontinued use of a prescribed PCA pump narcotic pain reliever because he reported a lack of need. Despite continued access to prescribed pain relievers, the patient declined due to lack of need. The patient was walking on Day 1, went home on Day 3, and resumed normal routine without pain on Day 10. The blinded study compound was APM (19.5 milligrams per tablet).

Example 6: Myocardial Infarction - Pain Alleviation

Pain associated with myocardial infarction has been associated with platelet aggregation. Since the pain reliever effects of APM show properties in common with aspirin and other nonsteroidal anti-inflammatory agents, APM was further evaluated for possible anticoagulant properties.

A preliminary study of bleeding times in twelve normal subjects was performed. After baseline bleeding times were measured using the Simplate bleeding technique according to manufacturer's instructions (General Diagnostics, Organon Technica, Oklahoma City,

OK), each subject ingested four tablets of aspartame (76 milligrams; 19 milligrams/tablet). Two hours after the oral ingestion of APM, repeat bleeding times were determined. The initial data demonstrated that a clinical response occurred in subjects with bleeding times of less than six minutes. Bleeding times longer than six minutes were thought to represent limits from commonly ingested dietary substances with properties similar to APM.

Since the preliminary data indicated possible clinical effects of APM on bleeding times, a double blind crossover study of 34 volunteers was conducted using the Simplate bleeding technique. All seventeen volunteers receiving placebo and seventeen receiving APM completed the study without complication. After a baseline bleeding time determination, each volunteer was given either four tablets of APM (76 milligrams; 19 milligrams/tablet) or four tablets of placebo.

Two hours after dosing, the bleeding time was repeated. Each bleeding time determination used pre-weighed blotting paper to collect blood droplets. The blotting paper was weighed on an analytical balance after the bleeding stopped. The time required for the bleeding to stop was measured with a stop watch. The data for the APM and placebo volunteers are given in Table X and Table XI, respectively. The effects of APM on bleeding time is summarized in Table XII and in Fig. 9 and Fig. 10. The results show a slight prolongation of bleeding time with APM which is similar to the

Table X. Bleeding Times Before and After APM

Subject	Before APM				After APM			
	Bleeding Time (min)	Pre-bleeding Wt (gram)	Post-bleeding Wt (gram)	Blood loss (gram)	Bleeding Time (min)	Pre-bleeding Wt (gram)	Post-bleeding Wt (gram)	Blood loss (gram)
1	4.460	4.669	4.769	0.120	4.430	4.692	4.850	0.158
2	5.150	4.728	4.819	0.091	4.420	4.726	4.890	0.164
3	3.430	4.720	4.811	0.091	5.140	7.991	8.142	0.151
4	3.220	4.285	4.333	0.048	4.000	4.764	4.831	0.067
5	5.030	4.781	4.889	0.108	5.250	4.803	4.884	0.081
6	5.340	4.781	4.978	0.197	4.060	4.704	4.778	0.074
7	3.540	4.790	4.841	0.051	4.250	4.748	4.848	0.100
8	5.060	5.608	5.723	0.115	6.070	5.200	5.307	0.107
9	5.320	5.189	5.309	0.120	6.450	5.466	5.950	0.484
10	4.270	5.215	5.325	0.110	5.490	5.166	5.464	0.298
11	4.330	5.400	5.550	0.150	5.290	5.418	5.578	0.160
12	4.440	5.595	5.727	0.132	5.090	5.735	5.873	0.138
13	2.370	5.442	5.451	0.009	2.050	5.586	5.605	0.019
14	3.320	5.508	5.548	0.040	3.380	5.361	5.372	0.011
15	3.380	6.015	6.040	0.025	4.060	5.792	5.825	0.033

Subject	Before APM				After APM			
	Bleeding Time (min)	Pre-bleeding Wt (gram)	Post-bleeding Wt (gram)	Blood loss (gram)	Bleeding Time (min)	Pre-bleeding Wt (gram)	Post-bleeding Wt (gram)	Blood loss (gram)
16	4.220	5.532	5.640	0.108	5.020	5.608	5.819	0.211
17	4.220	8.053	8.087	0.034	6.270	7.971	8.432	0.461
Average	4.182			0.091	4.748			0.160

Table XI. Bleeding Times Before and After Placebo

Subject	Before Placebo				After Placebo			
	Bleeding Time (min)	Pre-bleeding Wt (gram)	Post-bleeding Wt (gram)	Blood loss (gram)	Bleeding Time (min)	Pre-bleeding Wt (gram)	Post-bleeding Wt (gram)	Blood loss (gram)
1	3.270	4.690	4.735	0.045	4.530	4.656	4.755	0.099
2	4.480	4.735	4.858	0.123	3.270	4.731	4.793	0.062
3	3.550	4.707	4.771	0.064	3.360	4.691	4.726	0.035
4	4.300	5.404	5.461	0.057	4.040	5.927	5.960	0.033
5	4.510	4.766	4.952	0.186	6.440	4.731 3.747	5.171 3.852	0.545[a]
6	4.560	5.545	5.643	0.098	4.180	4.723	4.788	0.065

Subject	Before Placebo				After Placebo			
	Bleeding Time (min)	Pre-bleeding Wt (gram)	Post-bleeding Wt (gram)	Blood loss (gram)	Bleeding Time (min)	Pre-bleeding Wt (gram)	Post-bleeding Wt (gram)	Blood loss (gram)
7	5.230	5.480	5.609	0.129	5.180	5.658	5.789	0.131
8	4.500	5.403	5.479	0.076	4.040	5.366	5.426	0.060
9	3.160	5.325	5.417	0.092	3.380	5.354	5.505	0.151
10	3.420	5.418	5.515	0.097	3.430	5.251	5.388	0.137
11	4.270	5.375	5.510	0.135	3.440	5.434	5.500	0.066
12	2.470	5.328	5.380	0.052	2.220			0.000[b]
13	3.180	5.208	5.284	0.076	5.120	5.473	5.572	0.099
14	4.280	5.648	5.696	0.048	4.580	5.424	5.519	0.095
15	3.490	5.917	5.974	0.057	5.450	6.066	6.148	0.082
16	5.070	5.857	6.035	0.178	4.200	5.897	5.971	0.074
17	4.320	7.962	8.145	0.183	3.350	8.047	8.149	0.102
Average	4.004			0.100	4.130			0.080

[a] Two separate blotter papers used to absorb volunteer's blood; since total blood loss was outside of normal range, blood loss value not included in mean analysis.

[b] Volunteer did not bleed.

Table XII. Summary of Bleeding Time by Event and Mean Values

Treatment Group	Bleeding Time		Number of Patients	
	Before	After	Increased Bleeding Time	Decreased Bleeding Time
APM	4.18	4.78	13	4
Placebo	4.04	4.13	8	9

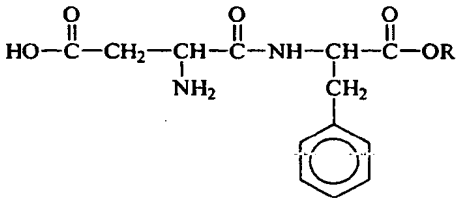
effect associated with aspirin. In the APM group, 13 volunteers had increased bleeding time, compared to 8 volunteers in the placebo group. By increasing bleeding time, APM may be used to control platelet aggregation and alleviate pain associated with myocardial infarction.

Example 7: Use of APM as a Veterinary Pain Reliever

A fifteen year old German shepherd dog experiencing osteoarthritic symptoms was given 5-10 tablets APM (95-190 milligrams; 19 milligrams/tablet) twice a day. Three days later, the dog had resumed normal activities. When the treatment was subsequently discontinued, the dog again exhibited osteoarthritic symptoms and lack of appetite. Treatment with APM was resumed, and the dog again resumed normal activity.

We claim:

1. A method of decreasing pain in a mammal comprising administering to said mammal in need of such treatment an effective amount of a compound comprising:



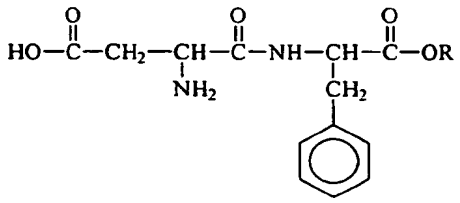
where R is H or an alkyl containing 1 to 6 carbons to affect a reduction of pain in said mammal.

2. The method of claim 1, wherein said effective amount of said compound is from about 40 milligrams to about 540 milligrams.

3. The method of claim 1, wherein an effective amount of said compound is from about 80 milligrams to about 320 milligrams.

4. The method of claim 1, wherein an effective amount of said compound is about 180 milligrams.

5. A method of decreasing the dosage of a first analgesic medication in a mammal for pain, comprising administering to said mammal in need of such treatment an effective amount of a second compound comprising:



where R is H or an alkyl containing 1 to 6 carbons to cause a reduction of pain in said mammal.

6. The method of claim 5, wherein said first analgesic medication is selected from the group consisting of acetaminophen, phenacetin, aspirin, ibuprofen, phenylbutazone, indomethacin and derivatives, opiates and derivatives, piroxacam, and steroidal and nonsteroidal anti-inflammatory agents.

7. The method of claim 5, wherein said effective amount of said second compound is from about 40 milligrams to about 540 milligrams.

8. The method of claim 6, wherein said effective amount of said second compound is from about 40 milligrams to about 540 milligrams.

9. The method of claim 5, wherein an effective amount of said second compound is that amount required

to reduce the effective dosage of said first analgesic medication by about 25% to about 75%.

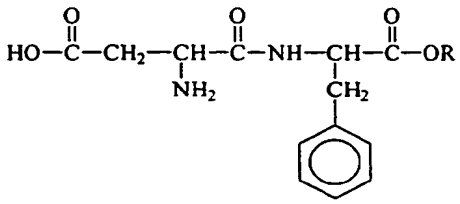
10. The method of claim 6, wherein an effective amount of said second compound is that amount required to reduce the effective dosage of said first analgesic medication by about 25% to about 75%.

11. The method of claim 5, wherein an effective amount of said second compound is that amount required to reduce the effective dosage of said first analgesic medication by about 10% to about 90%.

12. The method of claim 6, wherein an effective amount of said second compound is that amount required to reduce the effective dosage of said first analgesic medication by about 10% to about 90%.

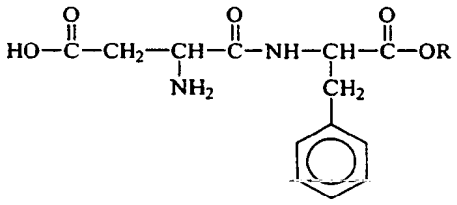
13. A method for treating an osteoarthritic mammal for pain, comprising the steps of:

administering an effective amount of a compound comprising:



where R is H or an alkyl containing 1 to 6 carbons to cause a reduction of pain in said mammal.

14. A pharmaceutical preparation in dosage unit form adapted for administration to obtain an analgesic effect, comprising, per dosage unit, an analgesically effective non-toxic amount of a compound comprising:



where R is H or an alkyl containing 1 to 6 carbons and a pharmaceutical carrier.

15. The pharmaceutical preparation of Claim 14, wherein said effective non-toxic amount is from about 40 milligrams to about 540 milligrams.

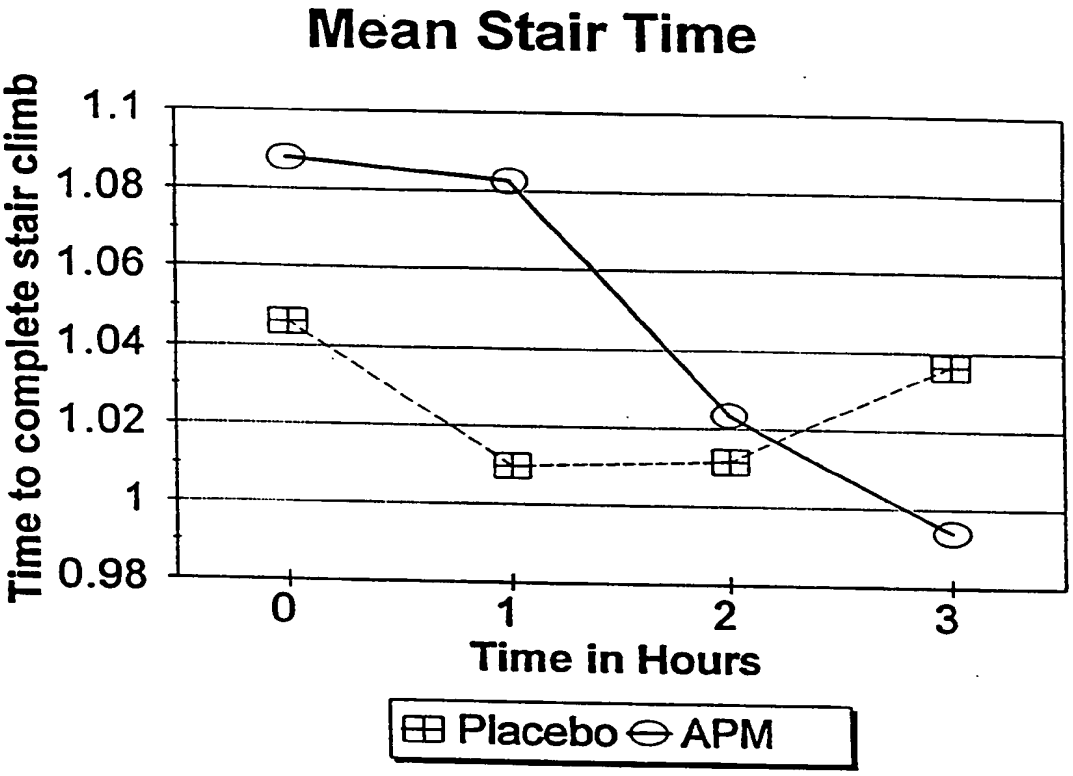


Fig. 1

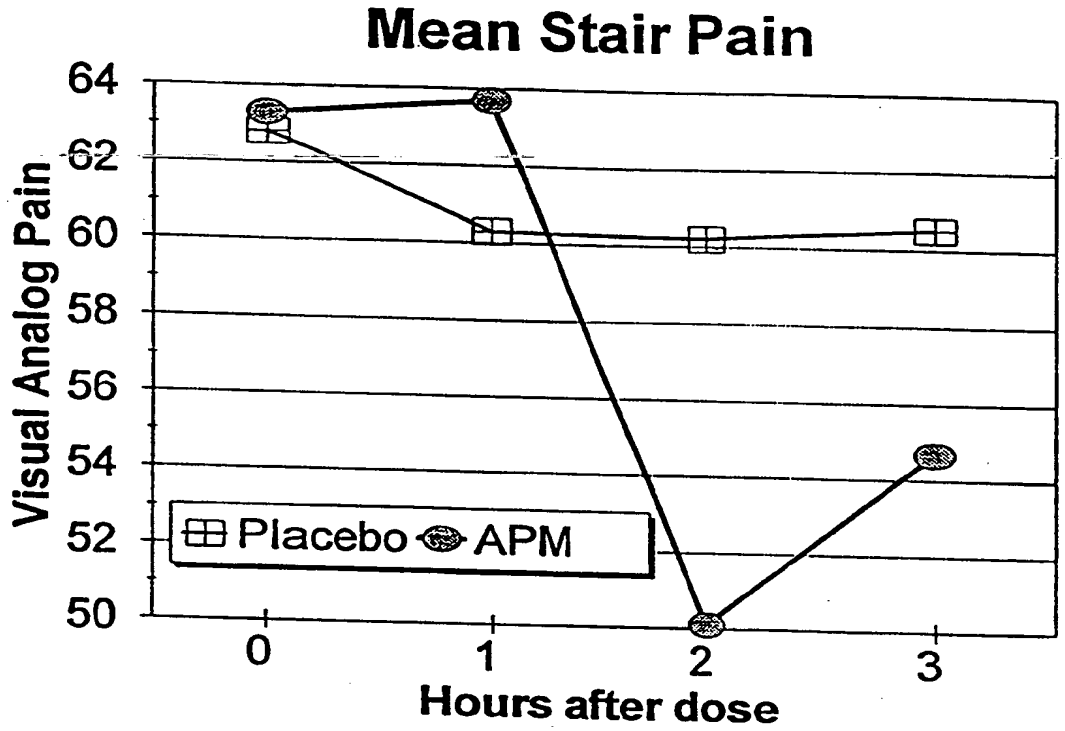

Mean Stair Pain
Visual Analog Pain
64
62
60
58
56
54
52
50
Placebo
APM
0
1
2
3
Hours after dose

Fig. 2

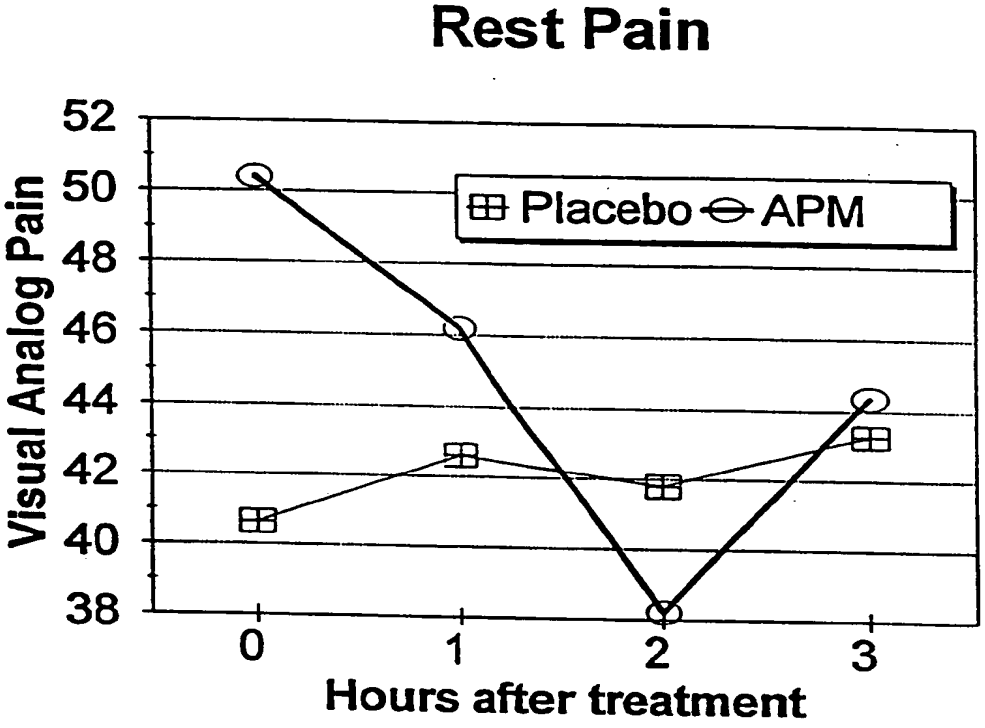


Fig. 3

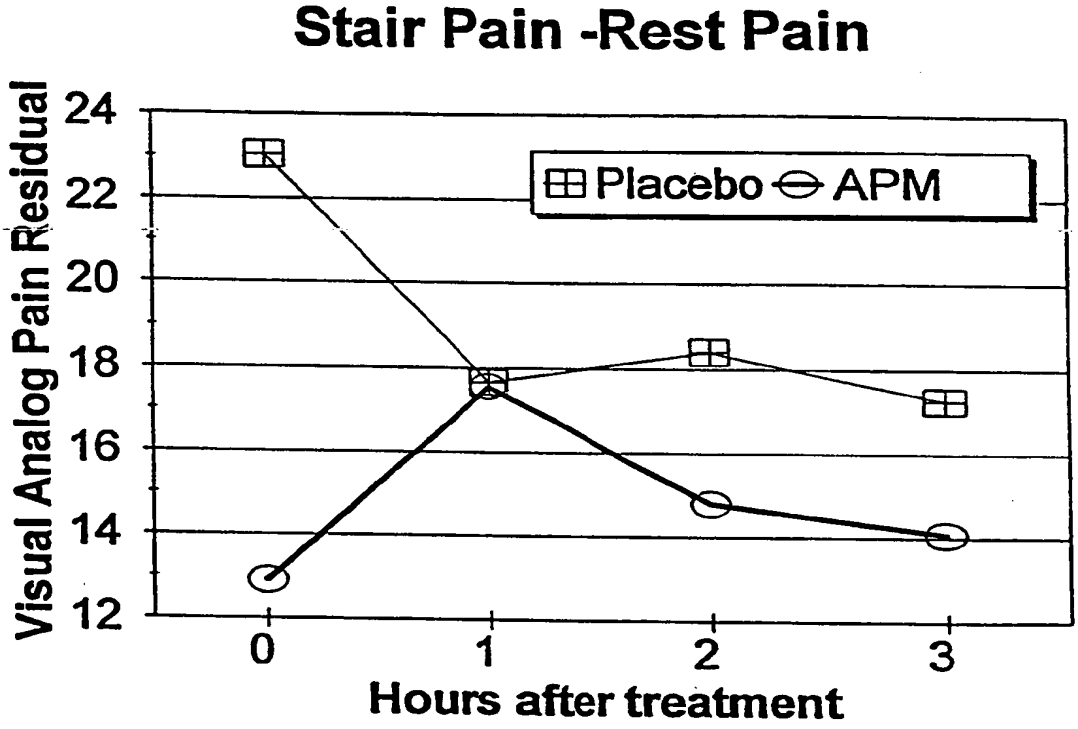

Stair Pain -Rest Pain
Visual Analog Pain Residual
24
22
20
18
16
14
12
Placebo
APM
0
1
2
3
Hours after treatment

Fig. 4

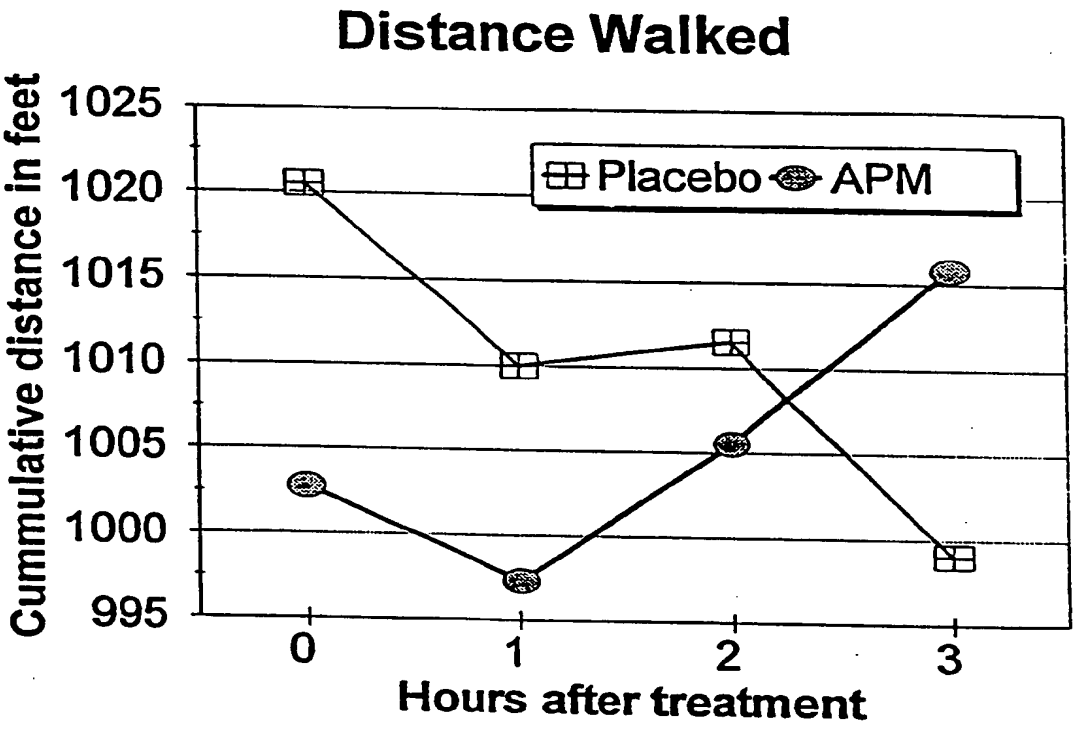

Distance Walked
Cummulative distance in feet
1025
1020
1015
1010
1005
1000
995
Placebo
APM
0
1
2
3
Hours after treatment

Fig. 5

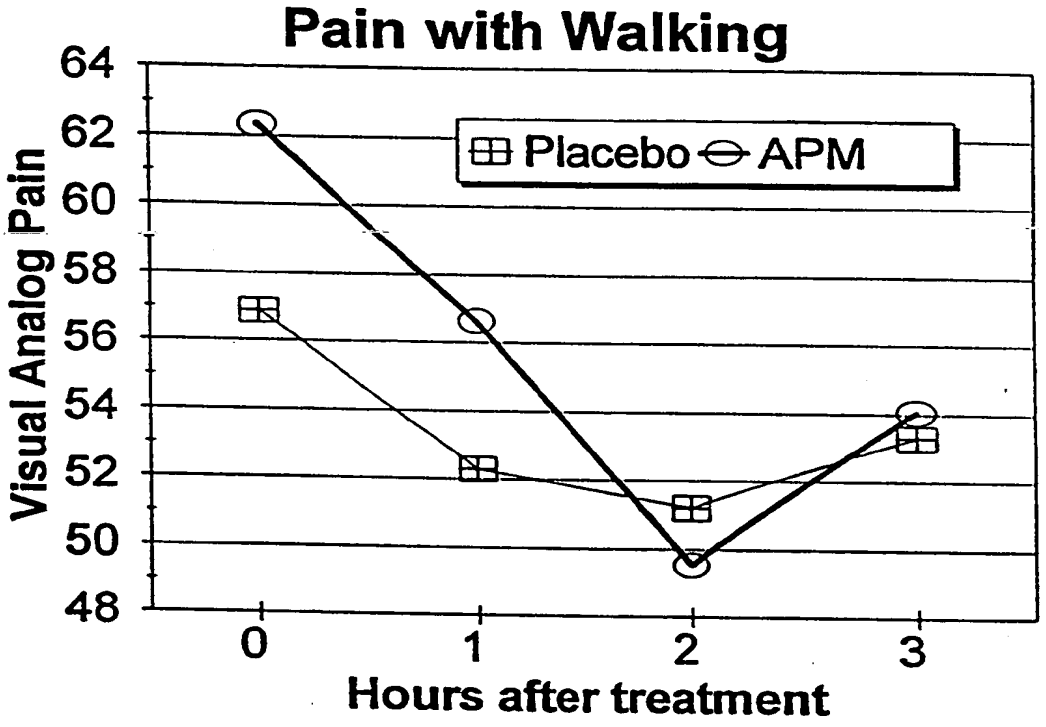

Pain with Walking
Visual Analog Pain
64
62
60
58
56
54
52
50
48
Placebo
APM
0
1
2
3
Hours after treatment

Fig. 6

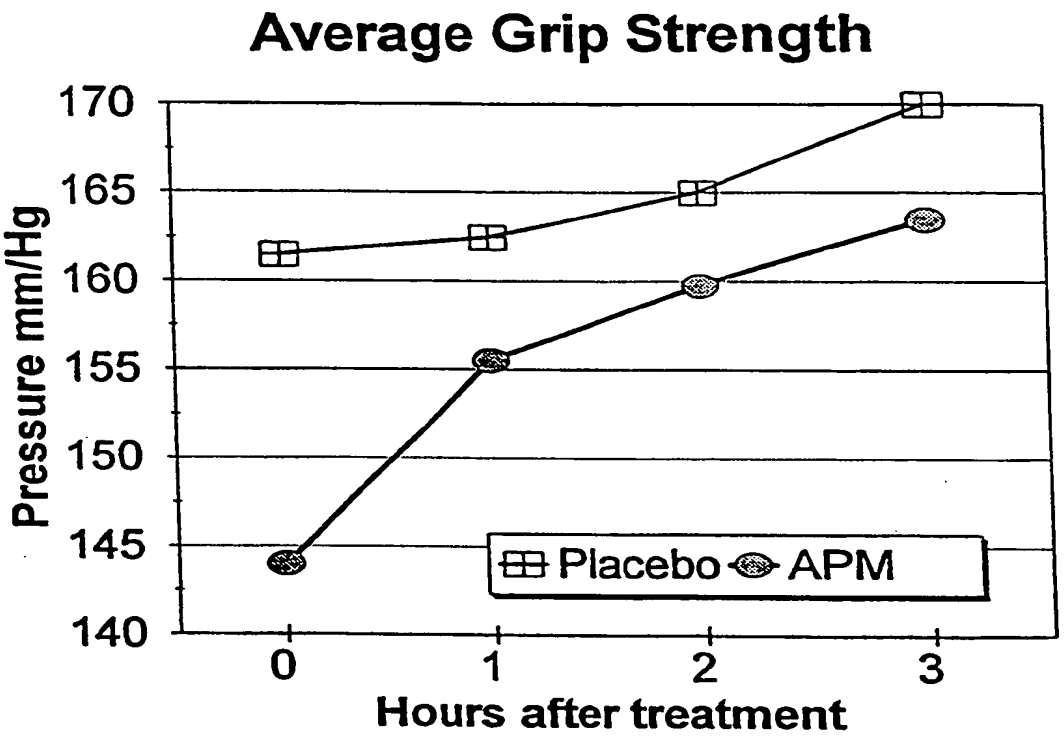


Fig. 7

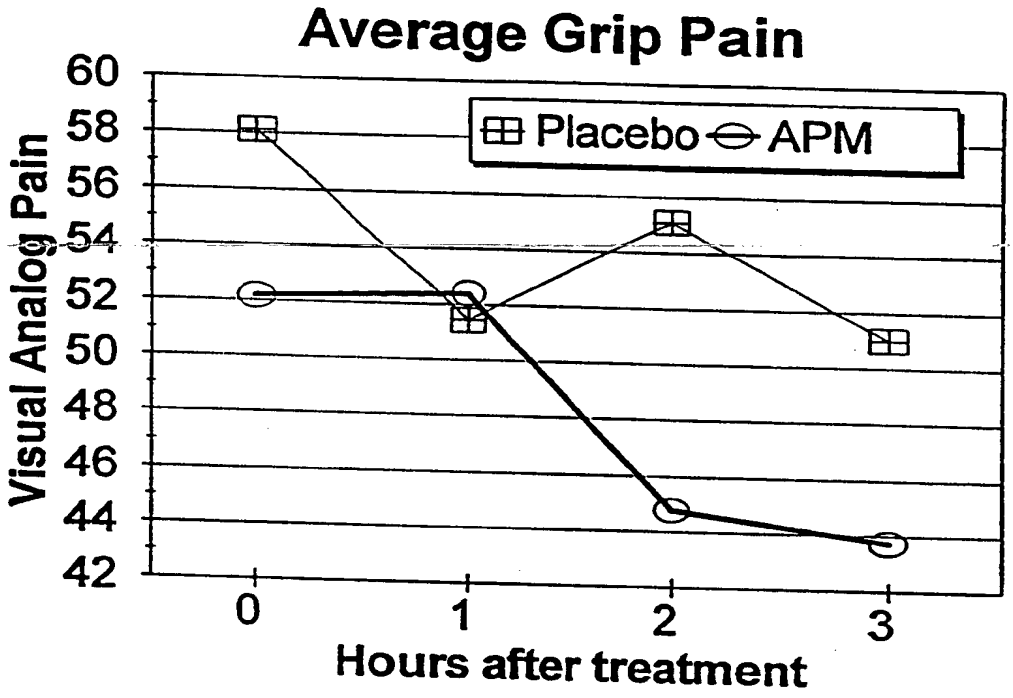

Average Grip Pain
Visual Analog Pain
60
58
56
54
52
50
48
46
44
42
Placebo
APM
0
1
2
3
Hours after treatment

Fig. 8

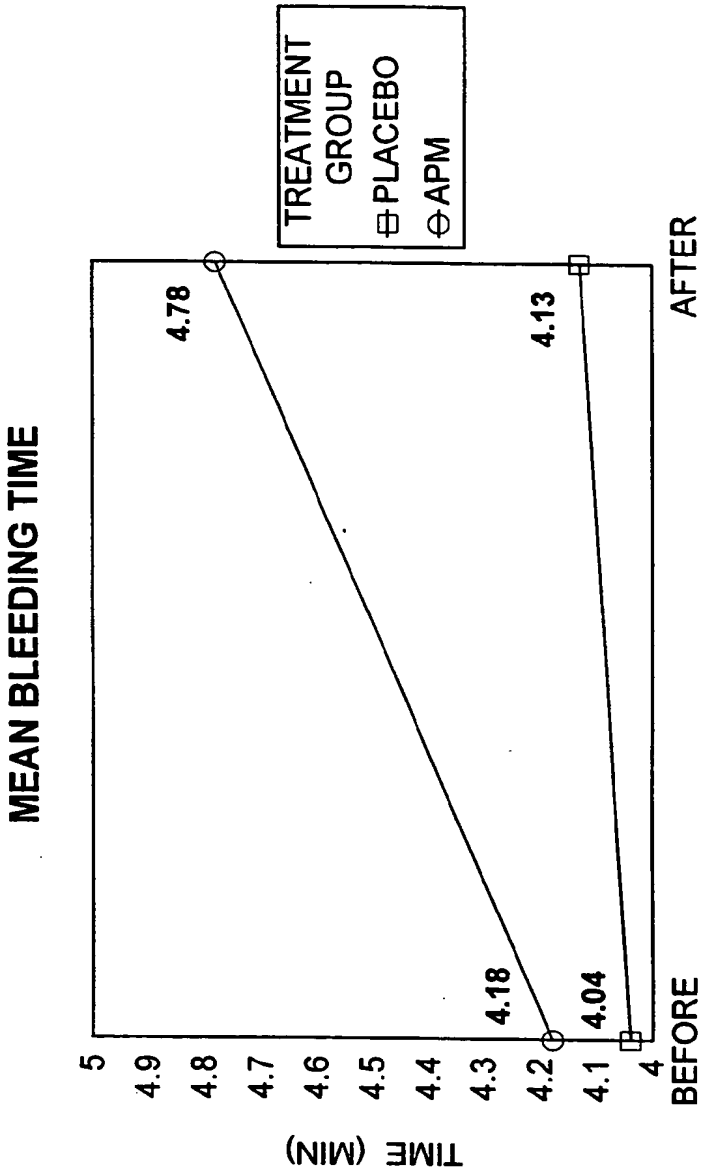


Fig. 9

10/10

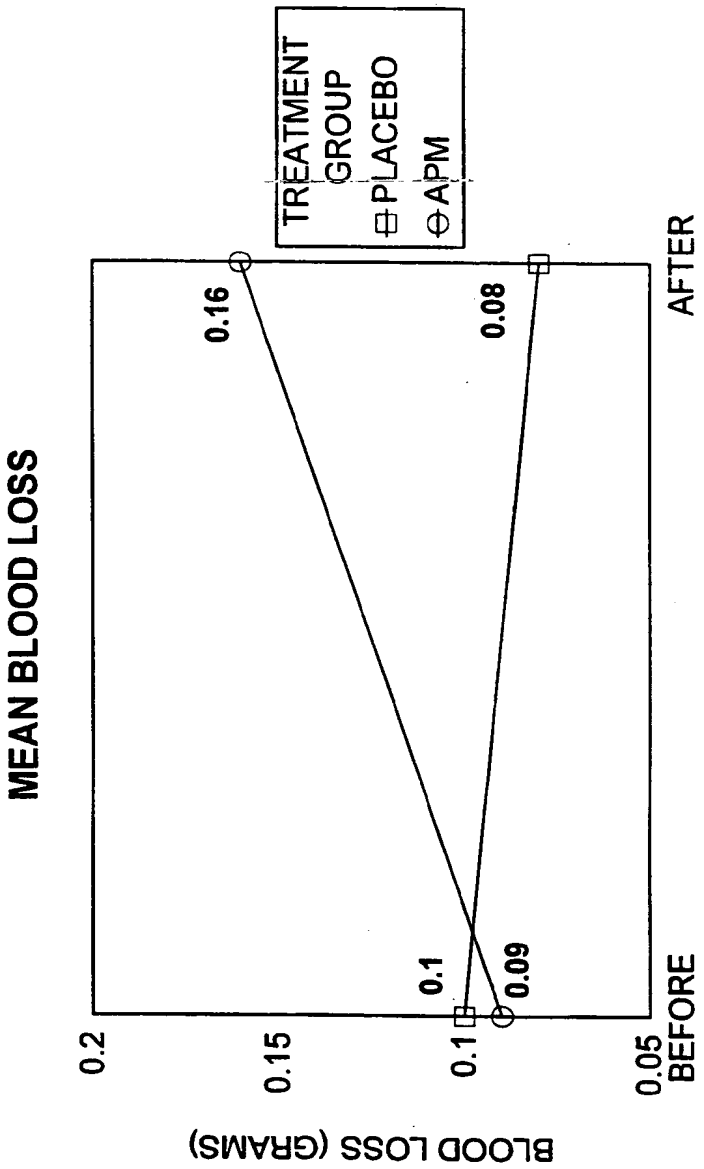


Fig. 10

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/10716

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/05 //(A61K38/05,31:165),(A61K38/05,31:60),(A61K38/05, 31:19),(A61K38/05,31:415),(A61K38/05,31:405),(A61K38/05,31:485), (A61K38/05,31:54),(A61K38/05,31:56)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,95 14486 (J. MESSADEK) 1 June 1995 see claims 1,9,23 ---	1-15
A	EP,A,0 468 121 (P. PEROVITCH ET AL.) 29 January 1992 see page 7, line 1 - page 8, line 25; claims 17-23 see page 9, line 44 - line 50 ---	1-15
A	GB,A,2 279 250 (ZAMBON GROUP S.P.A.) 4 January 1995 see examples 6-8,11,12 --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 1996	18. 10. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Ryckebosch, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/10716

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 112, no. 6, 5 February 1990 Columbus, Ohio, US; abstract no. 42621q, page 449; XP002014939 see abstract & JP,A,01 207 232 (MITSUI TOATSU CHEMICALS, INC.) 21 August 1989 -----	1-15

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/10716

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1 - 13 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Int[illegible]al Application No
PCT/US 96/10716

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9514486	01-06-95	BE-A-	1007099	14-03-95
		AU-A-	8054694	13-06-95
		EP-A-	0730468	11-09-96
EP-A-468121	29-01-92	FR-A-	2649611	18-01-91
		AU-A-	8316291	18-02-92
		EP-A-	0494297	15-07-92
		WO-A-	9201444	06-02-92
GB-A-2279250	04-01-95	BE-A-	1007194	18-04-95
		CA-A-	2125643	22-12-94
		DE-A-	4420856	22-12-94
		DK-A-	72594	22-12-94
		FR-A-	2706892	30-12-94
		JP-A-	7101855	18-04-95
		NL-A-	9401005	16-01-95
		NO-A-	942343	22-12-94
		SE-A-	9402157	22-12-94
		US-A-	5500226	19-03-96